antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2 and said disease is selected from the group consisting of systemic lupus erythematosus, thyroidosis, graft versus host disease, scleroderma, diabetes mellitus, Graves' disease, sarcoidosis, chronic inflammatory bowel disease, ulcerative colitis, disseminated intravascular coagulation, atherosclerosis and Kawasaki's pathology.

12 Cont

13

126. The method of Claim 125 wherein the anti-TNF chimeric antibody is cA2.

12

REMARKS

Claim Amendments

Claim 123 has been amended in an effort to advance prosecution. Claims 125 and 126 have been added. Support for Claims 125 and 126 are found throughout the specification, for example, page 61, lines 14-37 and page 62, lines 9-16. The amendments are made for the purpose of more clearly delineating that which Applicants regard as their invention. No new matter has been added. Entry is respectfully requested.

Obviousness-Type Double Patenting

Claims 110-124 were provisionally rejected under 35 U.S.C. § 101 as claiming methods that are not patentably distinct over Claims 91-97 of U.S. Patent 5,656,272. Applicants will file a Terminal Disclaimer upon resolution of the remaining rejections.

Rejection of Claims 123 and 124 Under 35 U.S.C. § 112, First Paragraph

Claims 123 and 124 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner maintains that while

"enabling for some immune and inflammatory diseases, [the specification] does not reasonably provide enablement for inflammatory diseases." (See page 3 of the Office Action). The Examiner further states that the art was, at the time of filing, unpredictable in treating septic shock, an inflammatory disease. The Examiner cites a review by Natanson *et al* (*Ann. Intern. Med.* 120:771-783 (1994)) to support his rejection. Applicants disagree.

The Examiner's reliance on the review article by Natanson *et al* as a basis for the rejection is misguided. Natanson *et al* do not teach, suggest or even mention the use of chimeric monoclonal antibodies to TNFα nor the generation of any specific monoclonal antibodies to defined epitopes of TNFα, which are the subject matter of the Applicants' claimed invention (e.g., cA2 antibody), as treatment for septic shock. While concerns regarding the clinical use of certain TNF antagonists are mentioned, it is clear that these concerns are specific for particular TNF antagonists, for example, murine monoclonal anti-TNF antibodies and recombinant human dimeric TNF receptors. (See page 776, first column, second and third paragraphs). The Examiner referred Applicants to the second column of page 776. A careful and thorough read of this paragraph reveals that the greatest apprehension, in terms of detrimental effects from TNF antagonist treatment, is the "[h]arm produced by <u>one</u> TNF antagonist [a recombinant human dimeric TNF receptor]" <u>not</u> chimeric monoclonal antibodies nor antibodies to specific epitopes of TNFα, as exemplified in the present invention (Emphasis added).

However, for the sole purpose of advancing prosecution, Applicants have amended Claim 123 to omit septic shock, the inflammatory disease reviewed by Natanson *et al*. Since Claim 124 depends on Claim 123, no amendment to Claim 124 is needed. In addition, inflammatory diseases which are enabled by the

specification (e.g., page 61, lines 14-37 and page 62, lines 9-16) are the subject matter for a method of treatment in newly added Claims 125 and 126. Accordingly, withdrawal of the rejection and reconsideration are respectfully requested.

Rejection of Claim 112 Under 35 U.S.C. § 112, Second Paragraph

Claim 112 has been rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the cA2 antibody. The Examiner insists that the cA2 antibody be referred to by an ATCC accession number. Applicants strongly disagree that the designation cA2 is indefinite and that deposition of the antibody be required to satisfy 35 U.S.C. § 112, second paragraph.
second paragraph.

The Examiner suggests that Applicants deposit the antibody or refer to the cA2 antibody by an amino acid or DNA sequence. Respectfully, Applicants disagree with the Examiner's static position in insisting on ATCC deposition of the antibody and on refusing to accept Applicants designation of a chimeric antibody as "cA2 antibody", which is extensively described in the specification. (See, for example, EXAMPLE I page 75, lines 16-34, and page 76, lines 1-30; EXAMPLE II page 77, lines 1-37, and page 78 lines 1-35; EXAMPLE V page 80, lines 19-34; EXAMPLE VII page 83, lines 29-35, and page 84 lines 1-17; EXAMPLE X page 85, lines 29-36, and page 86 lines 1-36; EXAMPLE XVI page 101, lines 30-36, and page 102, lines 1-35).

As discussed in several previous responses in this case, the cA2 antibody has not been deposited with the ATCC, and therefore, it has no ATCC accession number. As stated in the Manual of Patent Examining Procedure, § 2172.01, "[a] fundamental principle contained in 35 U.S.C. § 112, Second Paragraph, is that Applicants are their own lexicographer." In addition, "a claim may not be rejected solely because of the type of language used

to define the subject matter for which the patent protection is sought" § 2173.01. Applicants, in acting as their own lexicographers, created the designation cA2 for the specific chimeric anti-TNFα antibody disclosed in the application. The specification discloses activities of the antibody and the DNA (SEQ ID NOS: 2-5) and amino acid sequences of the heavy and light chain variable and constant regions of the cA2 monoclonal antibody in Figures 16A and 16B. The specification thereby defines the antibody and enables a person of ordinary skill in the art to produce cA2 and/or screen antibodies which have the same or similar properties without undue experimentation.

The term "cA2" must be read in light of the specification, not independently from the specification as the Examiner chooses to do in this application. The Examiner implies that the term may be used by other laboratories. Even if this were true, although highly unlikely, that subsequent use does not alter the definition of the terms provided in this application. That "factor" or possibility applies to all terms employed in claims, even routine or ordinary words.

Furthermore, in two related applications, Serial No. 08/192,102, now issued U.S. Patent No. 5,656,272, and Serial No. 08/324,799, now issued U.S. Patent No. 5,698,195, claims drawn to cA2 were granted by the Examiner. Frankly, Applicants do not understand why the Examiner allowed two patents reciting cA2 in the claims and his refusal to accept the term cA2 in Claim 112 of the instant application. Applicants are highly concerned with the confusing record the Examiner is creating. Accordingly, withdrawal of the rejection of Claim 112 is respectfully requested.

Rejection of Claims 110, 111, 113-118 and 123 Under 35 U.S.C. § 103.

Claims 110, 111, 113-118 and 123 have been rejected under 35 U.S.C. § 103 as being unpatentable over any one of either Aggarwal *et al* (U.S. Patent No. 5,672,347 (1997)) or Shalaby *et al* (*Transplantation*, 47:1057-1061 (1989)) or Brennan *et al* (*Lancet*, July 29:244-247 (1989)) or Piguet *et al* (*J. Exp. Med.*, 166:1280-1289 (1987); *J. Exp. Med.* 170:655-663 (1989)) or Grau *et al* (*Science*, 237:1210-1212 (1987)) each in view of Möller *et al* (U.S. Patent No. 5,231,024 (1993); *Cytokine*, 2:162-169 (1990)) or Rathjen *et al* (WO 91/02078 (1991)) each in combination with either Morrison *et al* (*Science*, 229:1202-1207 (1985)) or Morrison *et al* (*Hospital Practice*, October 15:65-80 (1989)). The arguments presented in the most recent Office Action mailed January 23, 1998, with the addition of Aggarwal *et al*, are verbatim from a previous Office Action mailed April 21, 1997 to which the Applicants fully responded to the Examiner's concerns in an Amendment mailed October 21, 1997. The Shalaby, Brennan, Piguet, Grau, Möller, Rathjen, and Morrison references were also discussed at length in other previous Amendments, which are incorporated herein in their entirety. It is noted that the Examiner does not acknowledge Applicants' previous arguments and provides no new basis to support this rejection.

Criteria for determining obviousness was set forth in Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1996). The scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art all indicate that Applicants' invention is not obvious.

Applicants' invention is drawn to methods of treating TNFα-mediated disease in a human comprising administering TNFα-inhibiting amounts of an anti-TNF chimeric antibody. Preferred claimed methods are directed to administering chimeric antibodies

which competitively inhibit binding of TNF to cA2; antibodies which bind to epitopes between 87-108 or both 59-80 and 87-108 of a specified amino acid sequence of hTNF; antibodies which do not bind to specified epitopes of hTNF; and antibodies comprising variable regions comprising specific amino acid sequences or comprising polypeptides encoded by specific nucleotide sequences. Also claimed are methods drawn to the use of anti-TNF chimeric antibodies comprising an IgG1 constant region.

The Shalaby, Brennan, Piquet, Grau, Möller, Rathjen, and Morrison references were discussed at length in several previous responses. It is noted with appreciation that in two related cases, Serial Nos. 08/192,102, and 08/324,799, now issued U.S. Patent Nos. 5,656,272 (1997) and 5,698,195 (1997) respectively, which contain claims similar to those in the present application (drawn to methods of treatment for Crohn's disease and rheumatoid arthritis with cA2 antibodies, respectively), were allowed by the Examiner. The claims in the 08/324,799 application (U.S. Patent No. 5,698,195 (1997)) were allowed over essentially the same references and their combinations. Again, Applicants are highly concerned by the inconsistencies in prosecution of these applications and the confusing record being created by the Examiner.

Applicants respectfully assert that the teachings of the references cited by the Examiner, either independently or in combination, do not support the conclusion that the claimed chimeric antibodies to TNFα are to be used in an expected and obvious manner.

Aggarwal *et al*

The Examiner states that Aggarwal *et al* (U.S. Patent No. 5,672,347 (1997)) teach therapy of graft rejections, arthritis; autoimmune and inflammatory diseases using anti-TNF antibodies; modes and doses of treatment; and IgG antibodies to TNF.

Applicants disagree that Aggarwal *et al* make the present invention obvious.

Aggarwal *et al* disclose the production and characterization of mouse monoclonal antibodies to human recombinant TNFα and the use of same to suppress, *in vitro* ^{3}H-thymidine incorporation in a mixed lymphocyte assay and, *in vivo* to decrease severity of the graft-vs-host reaction in a new born mouse model.

Aggarwal *et al* do not teach or suggest producing chimeric antibodies to TNFα. Moreover, the epitopes in human TNFα disclosed as preferred sites of variations by Aggawal *et al* are distinct from the epitopes of Applicants' claimed invention. For example, in column 5 Aggarwal *et al* list preferred epitopes in human TNFα which include amino acid residues 10-66, 113-134, 150-157, 1-40 and 40-66. The instant application is drawn to methods of treating diseases comprising humanized chimeric TNFα antibodies to epitopes of the TNF polypeptide at amino acid positions 87-108 or 59-80 and 87-108, none of which are taught or suggested by Aggarwal *et al*. Thus, Aggarwal *et al* teach away from the Applicants' claimed subject matter. Nothing in the report of Aggarwal *et al* would guide or motivate one of ordinary skill in the art to make the chimeric antibodies with the epitopic specificity of the Applicants' invention. In fact, Aggarwal *et al* would guide the artisan towards the production of different antibodies, from the epitopes taught by Aggarwal *et al*. Clearly such a lack of guidance does not support a rejection of obviousness under 35 U.S.C. § 103.

Moreover, Aggarwal *et al* do not teach a method of use of any TNFα antibody to effectively and unexpectedly treat a disease in humans as described in detail in the working examples of Applicants' invention (See, EXAMPLE XX, pages 105-116; EXAMPLE XXI, pages 116-119; EXAMPLE XXII, pages 119-135; EXAMPLE XXIII, pages 135-137). The mere report of a monoclonal antibody to a human TNFα with epitope specificity outside the teachings of the

instant invention and the use of same *in vitro* assays and *in vivo* mouse model systems, as disclosed by Aggarwal *et al*, does not make the Applicants' invention obvious and expected, taken alone or in combination with the references of record.

Shalaby *et al.*

The Examiner states the Shalaby *et al* (*Transplantation* 47:1057-1061 (1989)) teach methods of using anti-TNFα antibodies to prevent graft-verses-host disease (GVHD) in mice and suggests the same may be useful to treat humans. Applicants disagree that Shalaby *et al* render the instant application obvious.

Shalaby *et al* disclose the results of experiments designed to determine whether rabbit or hamster anti-recombinant murine TNFα antibodies would influence the development of graft-versus-host reaction (GVHR) in newborn BDF_1 mice injected with adult B6 spleen cells. The results of the experiments indicated that the inoculations with polyclonal or monoclonal antibodies to murine TNFα reduced spleen enlargement in the mice. Shalaby *et al* do not teach, suggest or even mention the use of chimeric monoclonal antibodies to TNFα, which is the subject matter of the Applicants' claimed invention. Shalaby *et al* do not teach or suggest producing monoclonal antibodies to specific epitopes of TNFα described in detail in the specification and working examples of the present invention. The hypothesis of Shalaby *et al* that "Antibodies to TNF-α may be a useful adjuvant for the treatment of GVHD" (Emphasis added page 60) does not provide one of ordinary skilled in the art with a reasonable expectation of success in making, and using TNFα chimeric monoclonal antibodies claimed in the Applicants' invention. Thus, the observations of Shalaby *et al* do not make obvious the present invention, taken alone or in combination with the references of record.

Brennan *et al*

The Examiner states that Brennan *et al* (*Lancet July 29*:244-247 (1989)) teach a method of using anti-TNFα antibodies to prevent IL-1 production in mononuclear cells from patients with rheumatoid arthritis and suggest that local injections of anti-TNFα antibodies may be useful in treatment of rheumatoid arthritis (Emphases added). Applicants disagree that Brennan *et al* make the present invention obvious.

Brennan *et al* describe a reduction in IL-1 production in synovial cell cultures from rheumatoid arthritis patients following *in vitro* incubation with rabbit anti-TNFα polyclonal antibody serum. Rabbit anti-TNFα did not have an effect on IL-1 production in synovial cell cultures obtained from osteoarthritis patients. Brennan *et al* state that the reason for this difference, despite a high TNFα concentration in both diseases, "is not fully understood", but that their results indicate that inhibition of IL-1 activity only occurs with the high initial IL-1 concentration present in the rheumatoid arthritis cultures. (pages 246-247). Significantly, they state that their results may indicate that other molecules found in rheumatoid arthritis patients, such as immune complexes or other cytokines, may synergise with TNFα and may be involved in IL-1 production (Emphases added page 246). They suggest that TNFα may damage rheumatoid joints directly and indirectly by IL-1 induction and may therefore be a target for therapy in rheumatoid arthritis (Emphasis added). Brennan *et al* do not provide any data from humanized chimeric antibodies to TNF-α or any epitope of TNF-α. Implicit in that is the lack of any discussion, teaching or suggestion of the production and use of same in the treatment of any disease as taught by the Applicants invention. Thus, the reports of Brennan *et al* do not render the Applicants invention obvious and expected. Based on the teachings of Brennan *et al* one of ordinary skill in the art would not be motivated to

practice and successfully administer the chimeric antibodies in the treatment of human diseases as taught in detailed in the present invention, taken alone or in combination with the references of record.

Morrison

The Examiner suggests that Morrison teach that chimeric antibodies were considered superior to rodent antibodies for *in vivo* therapies (*Hospital Practice, October* 15:65-80 (1989)) and that methods of making the antibodies were well established at the time of filing of the instant invention (*Science* 229:1202-1207 (1985)). Applicants disagree with this interpretation and maintain that the observations of Morrison do not make obvious the present invention.

Morrison discusses the possibility that chimerizing a murine antibody may decrease its immunogenicity and reports that murine/human chimeric antibodies have been made from, for example, anti-TNP mouse myeloma linked to human υ and κ genes.

Morrison does not teach the production of chimeric antibodies to any type of TNFα protein including any to specific epitopes of an antigen (e.g., TNFα) to treat disease. Rather, Morrison discloses a general method to generate chimeric antibodies and speculates on the projected or potential use of chimeric antibodies. Even Morrison concedes "The techniques and findings I [Morrison] have described are obviously those of a very young and very ambitious field" (See page 80, *Hospital Practice, October* 15:65-80 (1989)). The publication of a method to chimerize antibodies followed by a report of the potential applications of an untested technology does not teach in an enabling manner with a reasonable expectation of success the production of chimeric TNFα antibodies as described throughout the specification of the instant application. Even if one had extended the limited teachings of Morrison to the treatment of

diseases, there is absolutely no guidance on how to make and use the TNFα antibodies of the instant invention; nor any indication that chimeric TNFα antibodies are an effective and superior method of treatment for diseases as claimed in the instant application. Hence the reports of Morrison do not render the present invention obvious and expected, taken alone or in combination with references of record.

Rathjen *et al* and Möller *et al*

The Examiner suggests that Rathjen *et al* (WO 92/02078 (1991)) teach antibodies which inhibit biological activities of TNFα, and some of which bind to epitopes in the region of TNFα which contains an epitope recognized by the A2 antibody. The Examiner states that due to the relatively small size of TNFα and limited number of epitopes involved in receptor binding that the M195 antibody of Möller *et al* and some of the Rathjen antibodies would be expected to competitively inhibit binding of the A2 antibody of Applicants' invention. Applicants disagree. Neither the reports of Rathjen *et al* or Möller *et al* make obvious the claimed invention.

In order for a publication to render an invention obvious, the publication must describe the claimed invention with sufficient specificity and clarity so that one skilled in the art can make and use the claimed invention without assistance from the invention claimed to have been obvious. Neither the teachings of Rathjen or Möller regarding the production of monoclonal antibodies to human TNFα are enabling with respect to the Applicants' claimed subject matter and, therefore, do not teach with a reasonable expectation of success methods of treating TNFα mediated diseases in humans.

Möller *et al* (*Cytokine 2*:162-169 (1990); U.S. Patent No. 5,231,024 (1993)) disclose a specific murine monoclonal antibody, mAb 195 (M195), against human TNFα which neutralizes the

cytotoxic activity of human and chimpanzee TNFα in a murine cachexia model where a lethal dose of hTNF was administered. The Examiner states that, in view of the functional similarities between the A2 of the present invention antibody and Möller's M195 antibody, the A2 and M195 antibodies would be expected to recognize the same epitope or a closely related epitope. The Examiner admits that Möller *et al* do not teach chimeric anti-TNFα antibodies. (See page 8 of the Office Action). Yet, the Examiner suggests that the antibody neutralizing (e.g., TNFα) and binding (e.g., to human and chimpanzee) specificity, as well as the high affinity of both M195 and A2 antibodies support a "functional similarity" and "similar epitope binding specificities" between M195 and A2.

The present invention claims methods of treating TNFα-mediated disease by administering an effective inhibiting amount of an anti-TNFα chimeric antibody. Möller *et al* do not guide one of ordinary skill in the art to make chimeric antibodies (e.g., cA2) to successfully fulfill the long-felt need of treating the TNFα-mediated diseases of the claims as taught by Applicants' invention. Möller *et al* teach the generation of a mouse monoclonal antibody to human recombinant TNFα to treat cachexia or sepsis. The observation of Möller *et al* would not motivate the skilled artisan to chimerize murine antibodies and use them to treat other diseases. Möller *et al* would teach the artisan to make murine monoclonal antibodies to human TNFα. No teaching or suggestion in Möller regarding the murine monoclonal antibody M195 make the instant application expected or obvious.

Rathjen *et al* describe the production of monoclonal antibodies to recombinant human TNFα. The antibodies produced by Rathjen *et al* can, for example, inhibit the induction of clotting factors on the surface of endothelial cells, inhibit the binding of TNFα to its receptor and decrease the size of certain tumors in mouse animal models. While Rathjen *et al* may postulate that

monoclonal antibodies to human TNFα may ameliorate certain diseases (e.g., melanoma, breast cancer and bladder carcinomas), Rathjen *et al* do not teach methods of treatment for any human disease as claimed in and enabled by the instant invention. The mere suggestion that one of ordinary skill in the art could use the antibodies of Rathjen or Möller to treat human disease does not render the present invention obvious, taken alone or in combination with the cited references. The cited art including Rathjen and Möller provide no human clinical data of the successful treatment of human TNFα mediated diseases. There is no reasonable expectation of successful use of any antibody to TNFα including the monoclonal antibodies of Rathjen and Möller to treat other disease states. Further, the results described herein were unexpected. As such a *prima facie* case has not been established to support a rejection of obviousness. Therefore, withdrawal of the rejection is respectfully requested.

Piguet *et al*, 1987 and 1989

The Examiner states that Piguet *et al* teach methods of preventing and treating GVHD in mice which reduce mortality (*J. Exp. Med.* 166:1280-1289 (1987) and methods of treating pneumopathy and fibroses *(J. Exp. Med.* 170:655-663 (1989)) using anti-TNFα antibodies. Applicants disagree that the observation of Piguet *et al* (1987, 1989) make the instant application obvious or expected.

Piguet *et al;* describe the passive immunization of mice with IgG enriched fractions of a rabbit polyclonal antisera to TNFα. Following anti-TNFα treatment, significant decreases in indices of skin and intestinal lesions associated with acute phase GVHD (Piguet *et al*, 1987) and bleomycin-induced pneumopathy and fibrosis (Piguet *et al*, 1989) were reported. Piguet's observations utilizing rabbit polyclonal antibodies do not presuppose an expected use of monoclonal chimeric anti-TNFα

antibodies in human TNF-α-mediated disease as directed by the Applicant's invention. Notably, Piguet does not teach, suggest or even mention chimerizing monoclonal antibodies to TNFα to more effectively and reproducibly treat GVHD. Thus, the reports of Piguet *et al* do not made the Applicants' invention obvious or expected, taken alone or in combination with the references of record.

Grau *et al* (1987)

The Examiner states that Grau *et al* (*Science* 237:1210-1212 (1987)) teach a method of preventing cerebral malaria disease using anti-TNFα antibodies. Applicants disagree that the present invention is obvious in light of the observations of Grau *et al*.

Following a single intravenous injection of a polyclonal rabbit anti-murine TNFα IgG to *Plasmodium berghei* infected mice Grau *et al* describe full protection against cerebral malaria. The focal accumulations of macrophages containing erythrocytes, which were observed in the brains of control animals, were not seen in the brains of mice immunized with anti-TNFα antibodies. Grau *et al* do not teach, suggest or even mention the use of the claimed antibodies to TNFα for the treatment of diseases.

The report of Grau *et al* using *Plasmodium berghei* induced lesions in a mouse animal experimental model do not teach, with a reasonable expectation of success, the production of monospecific chimeric antibodies to TNFα and their use to effectively treat human diseases, which is the subject matter of Applicants' invention. In fact on page 1212 Grau *et al* state "this experimental model may not reproduce human CM [cerebral malaria]".

Brennan, Piguet, Grau - Polyclonal Antibodies

The polyclonal antibodies described in the teachings of Piguet *et al* (1987 and 1989), Brennan *et al* (1989) and Grau *et al*

(1987), are genuinely distinct from the preferred antibodies (monoclonal chimeric antibodies) in the Applicants' invention. Piquet, Brennan and Grau do not teach the production or use of monoclonal antibodies to specific epitopes of TNFα. The polyclonal antibodies of Grau, Piguet and Brennan are immunologically, molecularly and functionally different from the chimeric humanized monoclonal antibodies disclosed in the present specification. Polyclonal antibodies do not possess the structural and functional specificity of monoclonal antibodies. The polyclonal antibodies of Piguet *et al*, Brennan *et al* and Grau *et al* are, by definition, multiple ("poly") clonal and lack the reproducible response to a ("mono") clonal antibody. "Mono"clonal antibodies are chemically defined antibodies, unlike "poly"clonal antibodies. The specific and reproducible binding to a monoclonal antibody against TNFα is clearly a distinguishing feature of the cA2 antibody disclosed in the present application. Obviously, for reliable therapeutic treatment of TNFα diseases, a monoclonal antibody against TNFα, particularly to specific epitopes, is highly desireable. Piguet *et al*, Brennan *et al* and Grau *et al* do not teach or suggest the humanized monoclonal antibodies of the claimed invention (which are immunologically unique from polyclonal antibodies to TNFα), and, thus cannot teach or suggest methods of treatment with chimeric monoclonal antibodies as described throughout the specification and working examples of the instant invention. Therefore, the present invention is patentably distinct from Piguet *et al*, Brennan *et al* and Grau *et al* and is not taught or suggested by these reports which relate to the use of rabbit polyclonal antisera. Hence, the teachings of these references are even less relevant than those discussed above to the claims put forth in the present case and do not make obvious or expected Applicants' invention.

Improper Combination of References

The Examiner believes that, in light of the known limitations of murine monoclonal antibodies for human therapy, together with the expected advantages of chimeric antibodies, one of ordinary skill in the art would have been motivated to combine Morrison's, Rathjen's and Möller's teachings to produce chimeric antibodies which bind to an epitope of human TNFα, antibodies which neutralize TNF biological activity and antibodies according to the teachings of Möller *et al* or Rathjen *et al* and to select for those having the same functional properties as the M195 monoclonal antibody or the antibodies taught by Rathjen *et al* Further, according to the Examiner, the claimed antibodies do not appear to differ in any unexpected or unobvious manner from those that one of ordinary skill in the art would have expected to obtain in view of the teaching of Möller *et al* in combination with Rathjen *et al* Morrison to chimeric antibodies for the treatment of GVHD according to Shalaby *et al* (1989) and Piguet *et al* (1987) or rheumatoid arthritis as described by Brennan *et al* (1989) or pneumopathy and fibrosis as disclosed by Piguet *et al* (1989).

Applicants disagree. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. Id.

As discussed above, related application Serial No. 08/324,799 (1997) and U.S. Patent No. 5,656,272 (1997) were allowed and issued, respectively, over essentially the Examiner's same combination of references (or references cumulative to these references). Applicants note that in the previous Amendment mailed October 21, 1997 in response to the Office Action mailed from the PTO April 21, 1997, which is virtually verbatim identical to the present Office Action, Applicants' noted this inconsistency. The Examiner has remained tacitly silent on this matter. In appreciation of the Examiner's time and in the interest of brevity, the full text of the related arguments to the '799 and '272 cases has not been repeated. The following is included to emphasize the Applicants position.

In particular, the Examiner states that "Morrison teaches that chimeric antibodies were considered to be superior to rodent antibodies for use in in vivo therapies." It is pointed out that the Examiner does not provide the specific portion of the reference in support of this contention. Respectfully, this is a mischaracterization of the teachings of Morrison. Morrison states that the production of chimeric antibodies "may" help to solve the problem of HAMA responses upon human administration of non-human antibodies. "These potential advantages may be clinically exploited" (Emphasis added. page 78, *Hospital Practice October* 15:65-80 (1989)). "Chimeric molecules may prove useful... the application of the molecules to many clinical problems should be quite rewarding" (Emphasis added. page 1207, *Science* 229:1202-1207 (1985)). Neither the 1985 or 1989 Morrison citation provide any scientific data which might support these statements. In fact, it is clear from the clinical results provided in the specification and literature of record that chimeric antibodies also generate a "HAMA" response. Thus, it is clear that the Examiner's conclusion that the person

of ordinary skill in the art would be motivated to chimerize a murine antibody "to prevent human anti-murine antibody antibodies (HAMA)" is erroneous. It is noted that this position is partially retracted on page 14 of the action.

The Examiner states in the reasons for the rejection that TNF is "small and would be expected to possess a rather limited number of epitopes." Support for the assertion is not seen in this record and is apparently incorrect. Also, the relevance of the assertion is also not seen. To the extent that it relates to the issue of rejected Claims 110-112, 115-118 and 124 (which provide limitations relating to the epitopic specificity), it is clear that a number of antibodies are known in the art with distinct specificities and distinct properties. This is evidenced by Rathjen *et al*. There is no motivation provided by the Examiner to select antibodies which bind to the epitopes defined in each of these claims (from the numerous anti-TNF antibodies that can possibly be manufactured), much less the specific A2 antibody, for chimerization. Thus, the references relied upon by the Examiner do not render a method of treating TNFα mediated disease with the chimeric humanized monoclonal antibodies of Claims 110, 111, 113-118 and 123 as obvious and withdrawal of the rejection is requested.

Objective Evidence of Nonobviousness

As consistently recognized by the courts, the determination of nonobviousness must include, as relevant evidence, the "secondary considerations" of Graham v. John Deere, 383 U.S. at 17; 148 U.S.P.Q. at 467.

The secondary considerations described in Graham have been accorded significant weight by the Federal Circuit, as described in Glaros v. H.H. Robertson Co.: "The Federal Circuit has... repeatedly emphasized the importance of the inquiry into secondary considerations, such as the commercial success of the

invention and the prior failure of others, as the strongest precaution against judging an invention from the perspective of 20/20 hindsight." 224 U.S.P.Q. 1037, 1038 (N.D. Ill. 1984), aff'd 230 U.S.P.Q. 393 (Fed. Cir. 1986). Further, in Stratoflex, Inc. v. Aeroquip Corp., the Federal Circuit stated:

> [E]vidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness... Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983).

The secondary considerations set forth in Graham include, but are not limited to, unexpected results of the invention in relation to the prior art, expressions of disbelief by experts, and evidence that the invention has satisfied a long-felt need in the relevant field. The evidence regarding Applicants' invention clearly establishes all of these factors.

As indicated in Exhibits 1-3 and incorporated herein in their entirety, and as discussed in detail in the previous amendments including the most recent mailed October 21, 1997, researchers have performed clinical studies which demonstrate the safety and efficacy of administering the chimeric anti-TNF antibody cA2 to treat a TNF-mediated disease, rheumatoid arthritis (RA). The patients selected for the clinical studies had long-term, severe refractory disease and a history of failed therapy with several standard disease modifying anti-rheumatic drugs (DMARDs). Thus, the experiences of these patients clearly show long-felt and unsolved need for treatment for this potentially devastating disease well-recognized objective

criteria for nonobviousness. The fact that others in the field had tried for years to achieve a result, yet had failed, "is virtually irrefutable evidence that the [invention] would not have been obvious to those skilled in the art when it was invented." Panduit Corp. v. Dennison Mfg. Co., 227 U.S.P.Q. 337, 248-349 (Fed. Cir. 1985). Nonetheless, despite the duration and severity of their illnesses, the patients treated with chimeric anti-TNF antibody (cA2) experienced significant improvements and tolerated the treatments well, even upon multiple administration. (See, for example, Elliot *et al.*, *Arthritis & Rheumatism* 12:1681-1690 (1993), at 1685-1688; Elliott *et al.*, *Immunopharmac.* 17:141-145 (1995), at 142-144; Maini *et al.*, *Immunological Reviews* 144:195-223 (1995), at 206-211 (Exhibits 1-3, respectively)). These unexpected results in relation to the prior art are objective evidence of nonobviousness as set forth in Graham.

Furthermore, the magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art references. As noted in Exhibit 1 on page 1688, due to multiple and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce production of other cytokines and of themselves, there had been pessimism about whether targeting a single cytokine *in vivo* would have any beneficial effect. See, for example, Kingsley *et al.*, *Immunology Today* 12:177-179 (1991) (Exhibit 4) page 177

> [t]he most important question regarding cytokine intervention in rheumatic disease lies not in its technical feasibility but in the likely effect of interfering with only one cytokine within what is undoubtedly a very complex network. It seems highly improbable that a single cytokine holds the key to RA synovitis.

Trentham, *Current Science I SSN* 1040-8711:369-372 (1991)(Exhibit 5), page 370 "[t]he relevance of tumor necrosis factor and the biological outcome of its banishment by a monospecific inhibitor remain in doubt"; and page 371 "Unidimensional attacks on aberrant immune pathways might have limited effect on the underlying disease process".

Initial skepticism as to the merits of an invention by experts in the field supports the nonobviousness of this invention. Hughes Tool Co. v. Dresser Industries, Inc., 2 U.S.P.Q.2d 1396, 1402 (Fed. Cir. 1987). On page 13 of the Office Action the Examiner states that "Even if other cytokines were involved, a substantial activity of the pro-inflammatory cytokines IL-1 and TNFα are both reduced with anti-TNFα antibodies" and cites Elliot *et al.*, *Immunopharmacology* 17:141-145 (1995) and Maini *et al.*, *Immunol. Reviews* 144:195-223 (1995). Applicants respectfully disagree that the teachings of 1995 references can serve as standards for obviousness of this application which was filed in 1991.

Since the claimed invention has led to unexpected results, and clearly satisfies a long felt but unsatisfied need, the secondary considerations, as set forth in Graham, preclude a finding of obviousness. Furthermore, the prior art references do not describe or suggest Applicants methods of treating TNFα-mediated disease in humans by administering chimeric anti-TNF antibodies, do not provide a reasonable expectation of achieving such antibodies having reduced immunogenicity and a therapeutic benefit, and do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. Moreover, given the issuing of two related applications (U.S. Patent Nos. 5,698,195 (1997) and 5,656,272 (1997)) which contain claims and subject matter (e.g., methods of treatment with chimerized monoclonal antibodies such as cA2 to TNFα) similar to those in the present application, it is apparent that the

rejections based on § 103 have been overcome. Therefore, withdrawal of the rejection and reconsideration of Claims 110, 111, 113-118 and 123 are respectfully requested.

The Examiner's Response to Applicants' Remarks

The Examiner stated in the present and previous Office Actions that the Remarks made by Applicants were not convincing. Specifically, on page 11 of the Office Action the Examiner states that Applicants' argued "That the references themselves do not suggest the combination of the A2 epitope or any particular isotype." It is agreed that this is a part of the argument of record relating to the non-obvious selection of the epitope and/or the isotype relating to specific claims of record. Please note that each claim must be considered separately. The presentation of an argument relating to a dependent claim does not support the rejection of the independent claim. Regarding the Examiner's observation that there exists a possibility that the A2 epitope is the same or similar to the M195 epitope disclosed by Möller *et al* (1990)(1993)(*supra*), the Examiner does not address Applicants' argument. Even if the epitope is the same, there is nothing in the cited art which would teach or suggest that it would be desirable to select chimeric antibodies to TNFα which bind that specific epitope (from the many possible antibodies that can be generated) for chimerization as it is taught and documented as a successful treatment for the claimed diseases and working examples of the instant application. The Examiner's assertion that "routine" anti-TNF antibodies may also bind the A2 epitope is not understood. The fact that it is possible to raise antibodies which possess the same or similar epitopic specificity as the A2 antibody establishes that the claims are enabled for the full scope. It does not follow that it would therefore be obvious to select from all possible anti-TNF

antibodies those antibodies which possess the claimed epitopic specificities for chimerization.

Regarding the selection of the isotype (relating specifically to rejected Claims 113-118), the fact that different isotypes were known to possess different properties does not suggest that the selection of a specific isotype for the purposes of manufacturing an anti-TNF antibody for therapeutic purposes was obvious. There is nothing of record which might suggest that, in treating TNF-mediated diseases with an anti-TNF antibody, that the IgG1 isotype is desirable or advantageous. Applicants have provided evidence that the isotypes are not "equivalent", "mere alternatives" or "interchangeable", as the Examiner has characterized them. See Scallon *et al*, *Cytokine*, *7(3)*:251-259 (1995), discussed in more detail in a previous Response mailed March 10, 1997, which is incorporated herein in its entirety. The Examiner inappropriately employs hindsight in dismissing this evidence, stating that "One of ordinary skill in the art would have conducted a simple screening procedure or referred to the general wealth of knowledge in the art at the time the invention was made to select an isotype with the desired activities." (See pages 11 and 12 of the Office Action). Firstly, the Examiner has not provided a single reference at the time the invention was made which might suggest that one isotype would be advantageous over other isotypes for treating the claimed diseases. Thus, the latter portion of the Examiner's position is completely unsupported. Regarding the former portion of the Examiner's statement, the assertion that a screening could have been performed (or referring to the Examiner's earlier reference to the fact that methods for producing chimeric antibodies were known), does not support the conclusion that the result achieved by the claimed antibodies possessing an IgG1 isotype was expected. Please note that 35 U.S.C. §103 states that

"Patentability shall not be negatived by the manner in which the invention was made."

The Examiner then refers to Applicants' arguments relating to the fact that the references relied upon by the Examiner provide only *in vitro* and animal data. The Examiner apparently does not disagree with any of the technical observations made relating to each reference or the combination. However, he does, improperly, rely upon subsequently published results and observations.

Elliott *et al* (1995) and Maini *et al* (1995)

Specifically the Examiner states that in regards to Brennan *et al* (1989, *supra*), Elliott *et al* (1995, *supra*) and Maini *et al* (1995, *supra*) teach that *in vivo* therapeutic intervention in the treatment of rheumatoid arthritis using anti-TNFα antibodies was based on the *in vitro* teachings of Brennan *et al* (1989), *supra*. It is unfair to evaluate obviousness based upon the teachings of references published in 1995 which consider not just the teachings of Brennan but also the results of successful clinical trials. A skilled artisan, on the basis of the information disclosed at the time of the filing of the application in 1991, would not have been motivated to conclude that the *in vitro* teachings of Brennan *et al* (1989) would be obvious for *in vivo* treatments, as Elliott and Maini did in 1995.

The Examiner states that "The purpose of *in vitro* and animal experimentation is to provide one of ordinary skill in the art with a correlation or reasonable expectation of what would occur in a human." (See page 12 of the Office Action). Applicants do not disagree that such a correlation is desirable and is accurate in many instances. However, as the Examiner acknowledged, not all animal models correlate well. In fact, the Examiner, earlier in the prosecution of this application, asserted that animal models for treating septic shock cannot be

extrapolated at all. (For example, see page 3 of the Office Action mailed September 18, 1996.) Applicants have provided technical basis in support of the argument and have, thus, rebutted the Examiner's rejection. The Examiner has not acknowledged his inconsistency in the record nor has he acknowledged Applicants' technical data to refute his apparent misconceptions.

Applicants argued that the prior art suggested that the inhibition of a single cytokine would not necessarily be sufficient to alleviate the disease. In response, the Examiner reminds Applicants that "the claims are drawn to a method of treatment not a cure." (See page 13 of the Office Action). It is apparently the Examiner's position that even if the prior art taught that other cytokines are involved, a "substantial effect would have been expected." (See page 13 of the Office Action). There is no evidence of record which would support the Examiner's conclusion that the clinical effect achieved by TNF blockade as described in the Applicants invention would be "expected" to be "substantial", except for the subsequent clinical results achieved from the cA2 antibody of the present claims. Again, the Examiner's position is unsupported by the record. More specifically to the Examiner's point, it is agreed that the claims are not limited to a disease cure, but to a treatment of disease. Thus, even if some therapeutic benefit was expected from the cited art, the actual results achieved and reported herein were totally unexpected. Therefore, any *prima facie* case of obvious which may have resulted has been rebutted.

The Examiner refers to a decade of routine administrations of antibodies to humans as of the time the invention was made. (See page 13 of the Office Action). Applicants strongly take issue with the Examiner's unsupported assertion. The Examiner has repeatedly held to this unsubstantiated opinion in several Office Actions. He has not provided any documentation of his

opinion (e.g., references from artisans in the field) in response to Applicants' position that the Examiner has no basis for such a definitive and specific assertion. It is impossible, based upon such a vague assertion, for Applicants to place the human therapies as envisioned by this Examiner in their proper context. In any event, the fact is irrelevant to the issue. Therapies for treating TNF-mediated diseases in humans by the administration of anti-TNF antibodies were not known as the time the instant invention was made. Thus, the fact that antibodies other than chimeric TNFα antibodies in the treatment of other disease states were successful is not relevant to the issue of whether the person of ordinary skill in the art pertinent to the Applicants invention would reasonably expect the administration of a chimeric anti-TNF antibody (much less the specific anti-TNF antibodies defined by particular TNF epitopes which are the subject matter of Applicants' invention) to possess the therapeutic benefits described herein.

The Examiner points to the contents of the earliest claimed priority date, it is believed that the Examiner is attempting to state that the clinical results added in the later filed continuation-in-part applications cannot be relied upon to rebut the rejection. Of course, this is incorrect. See, for example, In re Davies, 177 USPQ 381 (CCPA 1973) which illustrates the point.

The Examiner states that "determining the pharmacokinetics of an antibody was routine" and "demonstration of specific binding and ability to neutralize is a good indication of the affects in vivo." (See page 14 of the Office Action). Even if this is true, it does not support the conclusion that the clinical result of the antibody would be as achieved and reported herein. Thus, the issue of whether the antibody will bind TNF *in vivo* is distinct from the issue of whether that

binding and any subsequent neutralization will be clinically beneficial (or how much of a clinical benefit can be expected).

The Examiner dismisses the teachings of Kingsley *et al* (*Immunology Today* 12:177-179 (1991) and Feldman (Elliott, Maini, Feldman *et al*, *Arthritis and Rheumatism* 12:1681-1690 (1993); Elliott, Feldman, Maini, *Immunophacmac* 17:141-145 (1995)) cited by Applicants to establish that persons in the art were skeptical about ability to treat diseases by TNF blockade. His reason appears to be in the fact that the Brennan *et al* and Shalaby *et al* articles are not cited therein. It is not clear precisely what the Examiner is referring and/or objecting to. In any event, Drs. Marc Feldmann and Ravinder Maini, were coauthors of the 1989 Brennan *et al* article (Brennan, Chantry, Jackson, Maini and Feldman, *Lancet July* 29:244-247 (1989)). Thus, it is unlikely that any subsequent articles by Drs. Feldmann and Maini were drafted "unaware" of their own earlier publications. In any event, the Examiner's observation that a journal article is not cited in a review article does not support the conclusion that the manuscript (or any manuscript substantially cumulative to or more relevant than the manuscript relied upon in the rejection) was not known to the authors or that the opinion of the authors would have been modified by those results. The case law clearly establishes that such teachings must be considered by the Examiner in evaluating obviousness.

In summary, the references relied upon in the rejection do not teach chimerizing an anti-TNF antibody, do not teach that the selection of particular epitopes and/or isotypes, and do not teach (with a reasonable expectation of success) that such antibodies would be clinically beneficial in treating TNF-mediated disease. Even if *arguendo*, it would have been obvious to manufacture a humanized chimeric antibody (e.g., with the claimed epitopic specificities and/or isotype) and administer

that antibody in the treatment of the disease states discussed in the rejection (e.g., shock resulting from GVHD), the references do not teach that the clinical results actually achieved would be expected. Therefore, withdrawal of the rejection, and reconsideration of claims 110, 111, 113-118 and 123 are requested.

Allowance of Claims 119-122

Applicants thank the Examiner for allowing Claims 119-122.

Request for Interview

Applicants hereby request an interview with the Examiner before issuance of the next Office Action.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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